REMARKS

Claims 7-10 remain pending in the application.

New claims 20-28 now presented further define and specify the method for treating metabolic bone disease, wherein the modulation of PTH and/or PTHrP is further defined as being through the modulation of PEX, as supported by the teachings and experimental evidence of the present application, where it is clearly shown for the first time, with enabling evidence, that PEX is the modulating compound that modulates PTH and/or PTHrP levels, and where the modulation of PEX, by any PEX-binding substrate affects or modulates the enzymatic activity of PEX, to effectively elicit the modulation of PTH and/or PTHrP levels, thereby providing a method of treating a metabolic bone disease.

Claims 7-10 currently stand as rejected for allegedly failing to meet the written description and enablement requirements pursuant to 35 U.S.C. § 112, first paragraph; and for being allegedly anticipated by Vickery et al. (US 6,583,114 B2) or Chorev et al. (WO 96/19246) pursuant to 35 U.S.C. § 102(e).

It is submitted that each basis for rejection is addressed below. Reconsideration of the rejections is respectfully requested in view of the following remarks.

Applicant respectfully submits that claims 7-10 of the present application relate to a mechanism of treating a metabolic bone disease by the modulation of PTH and/or PTHrP levels through PEX. As is clearly described in the specification, an underlying mechanism for such PTH/PTHrP modulation is the alteration in the bone micro-environmental concentration of critical bone anabolic agents, namely PTH and PTHrP, which are shown for the first time to be modulated by PEX enzymatic activity.

The teachings of the present application provide a clear written description and enabling evidence of the modulation of PTH/PTHrP by PEX. More specifically, the

present application provides evidence that PEX is the endopeptidase compound that is shown to cleave PTH and likewise PTHrP (please refer to page 24, last paragraph). In the description on page 24, PEX is shown to be an endopeptidase that cleaves PTH(1-34), PTH(1-38), and, as would be understood by one skilled in the present art who would readily observe the similarity of PTHrP with PTH, that PEX, as described in the present invention likewise, cleaves PTHrP. Accordingly, applicant respectfully submits that the modulation of PEX enzymatic activity therefore provides a means of modulating PTH/PTHrP levels, wherein this means of modulation has not been taught by the prior art, and is clearly described and enabled by the teachings of the present invention.

The present invention also provides that PEX has homology with NEP (neprilysin), thereby providing evidence that PEX is an endopeptidase and a member of the endopeptidase family, which also comprises ECE-1 and Kell antigen (please refer to page 17, lines 11-24; page 18, lines 26-27; page 23, lines 30-32; and Fig. 2B). It should also be noted that in addition to the above points, the present invention describes and provides enabling evidence that PEX is the compound, i.e. the endopeptidase compound, that modulates PTH/PTHrP, as is clearly described in the description (for example, on page 29, lines 1-3, lines 6-9, and lines 16-17). In view of the teachings of the present description and the evidence provided therein, it is respectfully submitted that the presently pending claims are clearly described and enabled by the written description and the results provided, to provide a method of treating a metabolic bone disease, wherein PEX is shown to be a modulator of PTH/PTHrP levels, and wherein the modulation of PEX effectively modulates PTH/PTHrP levels. Accordingly, based on the teachings of the present invention, and on the knowledge of one skilled in the art, the design of PEX inhibitors/modulators for the subsequent modulation of PTH/PTHrP levels may be accomplished, thanks to the finding of the present invention, wherein any PEX-binding substrate, such as any known inhibitors of NEP, for example, phosporamidon, which may affect PEX enzymatic activity may be used to modulate PEX activity, which would in turn modulate PTH/PTHrP levels and hence modulate bone formation and bone breakdown.

The present invention clearly provides one skilled in the art with a clear written description and means for the identification or design of PEX inhibitors for the modulation of PTH/PTHrP levels, wherein said PEX modulators are PEX binding substrates that modulate or affect PEX enzymatic activity. For example, on page 9 (lines 1-3) one skilled in the art would understand that an examination of PTH breakdown fragments allows for the determination of the cleavage sites of the PEX substrate, namely the cleavage sites of PTH/PTHrP, so as to thereby lead one skilled in the art to readily design PEX inhibiting compounds. Moreover, on page 1 (lines 31-35) the present application clearly describes the interactions between PEX-PTH, and likewise, page 8 (lines 24-35) clearly describes the mechanisms and interactions between PEX-PTHrP. It should also be noted that the present invention also provides for the use of inhibitors to PEX related enzymes. For example, the present invention also provides for the use of inhibitors to PEX related enzymes, as shown in the teachings of the present invention, that Naprilysin (NEP) is homologous to PEX, wherein a description of the structural relation of PEX to NEP is provided, and wherein NEP, like PEX is an endopeptidase. Accordingly, it would be understood, that an NEP inhibiting compound, such as phosphoramidon, could likewise be a PEX inhibiting compound. Accordingly, the present invention contemplates that known NEP inhibitors may additionally be PEX inhibitors; reference to page 1 (lines 14-17) and page 7 (lines 21-23) and also to Fig. 2B, which illustrates human PEX and human NEP protein alignments (SEQ ID NOs: 3-4), is made. Accordingly, in light of what is known in the prior art, and what is now provided in the teachings of the present application where PEX is shown to be the PTH/PTHrP modulating compound, it is understood and embodied in the present invention that any compound that modulates PEX, i.e. a PEX binding substrate that modulates or affects PEX enzymatic activity will accordingly modulate PTH/PTHrP levels.

As noted above, the present application additionally teaches that PEX has homology to members of membrane bound metalloendopeptidase enzymes, such as ECE-1 and Kell antigen, as described on page 17 (lines 11-20). PEX has also been shown to require zinc (Zn) in the allosteric site for catalytic proteolytic activity. Accordingly, based on the teachings of the present invention and the evidence provided therein, one skilled in

the art would recognize metal chelators, such as 0-phenanthroline, to be a potential PEX inhibitor for the development of novel agents to treat metabolic bone disease based on the mechanisms provided in the present application. Accordingly, applicant respectfully submits that the subject matter of the present application and the presently pending claims adequately describes the subject matter to one skilled in the present art.

Furthermore, in connection with the rejections regarding the alleged lack of enablement for claims 7-10, applicant respectfully submits that the present application clearly describes the modulation of PTH/PTHrP levels. Furthermore, the present application provides a clear and enabling description for the modulation of PTH/PTHrP levels through PEX, and accordingly the modulation of PEX. Moreover, the present invention also teaches and describes the homology between PEX and NEP, wherein said homology would allow and provide sufficient instruction for one skilled in the art to formulate a therapeutically effective dose of a known inhibitor of NEP, such as Phosphoramidon, for the use in the modulation or inhibition of PEX so as to accordingly modulate PEX and subsequently modulate PTH/PTHrP levels so as to promote bone formation and to treat metabolic bone disease.

Regarding the Office Actions' comments regarding the cloning of PEX and gene therapy, applicant respectfully submits that the subject matter of the presently pending claims relates to a method of treating metabolic bone disease by the modulation of PTH/PTHrP levels. It is respectfully submitted that the cloning of PEX encoding cDNA, in the context of the presently elected and examined claims, would be understood by one skilled in the art to relate to a method of treating metabolic bone disease by the modulation of PTH/PTHrP levels through the modulation of PEX. In fact, one skilled in the art would understand that the cloning of the human full length PEX cDNA in the context of the present application, in effect provides a tool for examining and gaining additional insight into the role of PEX in normal physiology for the study of PEX in tissue expression, subcellular localization and peptidase activity, as clearly described on page 1 (lines 10-14) of the present application. The use of cloned PEX cDNA, as shown in the present

application, confirms the size of PEX, PEX's trans-membrane localization on osteoblasts, PEX's homology with Neprilysin, PEX's almost exclusive expression in osteoblasts, as well as PEX's peptidase activity, as shown for the first time in the present application, wherein PEX acts as a peptidase used to cleave, for example, PTH(1-34). Accordingly, applicant respectfully submits that the commentary relating to the cloning of PEX cDNA and gene therapy would be understood by one skilled in the art to not apply to the presently examined pending claims.

Accordingly, applicant respectfully submits that the teachings of the present invention sufficiently describe a method for modulating PTH/PTHrP levels for the treatment of metabolic bone disease wherein said modulation of PTH and/or PTHrP is clearly described as being effected through the modulation of PEX. The present application also provides sufficient description and enabling evidence to enable one skilled in the art to use a compound for the modulation of PTH and/or PTHrP levels wherein said compound, based on the reading of the present application, is a compound that modulates the enzymatic activity of the PEX.

Accordingly, applicant respectfully requests reconsideration and withdrawal of the rejections to claims 7-10 under 35 U.S.C. § 112, first paragraph.

In connection with the rejection of claims 7-10 under 35 U.S.C. § 102(e), where it is noted that claims 7-10 are allegedly anticipated by Vickery et al. and/or Chorev et al. Applicant respectfully submits that Vickery et al. relates to the healing of fractures using PTHrP analogs, and not to the modulation of PTH/PTHrP levels through the modulation of PEX. The teachings of Vickery et al. completely differ from the teachings of the present application, primarily due to the fact that, in the present application, the modulation of PEX enzymatic activity accordinlgy modulates PTH/PTHrP levels, which in turn promotes the modulation of endogenous bone micro-environmental concentrations of PTH/PTHrP, as opposed to the compounds described by Vickery et al., where PTHrP analogs, are exogenous compounds that have nothing to do with PEX activity. Accordingly, applicant

respectfully submits that Vickery et al. does not anticipate the novel mechanism of modulating PTH/PTHrP levels by PEX modulation. Accordingly, applicant respectfully requests that the rejections in view of Vickery et al. be reconsidered and appropriately withdrawn.

Similarly, in view of the objections to claims 7-10 under Chorev et al., it is respectfully submitted that Chorev et al. describes the administration of PTH or agonists for promoting bone formation. Accordingly, applicant respectfully submits that the teachings of Chorev deviate from the teachings of the present invention, and in fact have nothing to do with the modulation of endogenous levels of PTH/PTHrP levels by the modulation of PEX enzyme for the purpose of providing a novel method of treating metabolic diseases, as described in the present application. Likewise, applicant respectfully submits that claims 7-10 are not in any way anticipated by Chorev et al. Accordingly, applicant respectfully requests that rejections under 35 U.S.C § 102(e) be reconsidered and appropriately withdrawn.

It is believed that in view of the remarks provided above, the rejections raised against presently pending claims 7-10 be reconsidered and accordingly withdrawn. It is also submitted that the newly provided claims are fully supported and enabled by the teachings of the present invention, and are unanticipated by the prior art.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

By Joseph C Zucchero

Dated: June 22, 2004

Joseph C. Zucchero
Registration No. 55,762
Attorney for Applicant

Keown & Associates
500 West Cummings Park
Suite 1200
Woburn, MA 01801
Telephone: 781/938-1805
Facsimile: 781/938-4777